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Commentary

From Bench to Bedside: Unique Challenges of Treating Epilepsy in the Aging Brain

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As the baby-boomer generation ages, as much as 20% of the U.S. population will be older than 65 [1]. The elderly population has the highest susceptibility to seizure disorders [2,3] and treating these seizures presents a unique set of circumstances because the aged brain is anatomically different than the young adult brain. Most antiepileptic drugs (AEDs) were designed for and tested in either pediatric or young adult patients, but not in geriatric patients. This discrepancy between the aged and young adult brain is further complicated by the fact that elderly patients often have co-morbid conditions and take one or more medications. Each of the medications affects the hepatic enzyme system and multi-drug interactions can result in altered responsiveness to AEDs. Furthermore, the elderly population has a high probability of developing status epilepticus (SE) and status-related death [4,5]. Thus, it is vital to examine how the late-life brain is altered following seizures, so that safer and more efficacious treatments will be available to the increasingly large, elderly population. This concept is elegantly introduced in the first article of this special edition, where Verellen and Cavazos [6] highlight the unique pathophysiological considerations of seizures and epilepsy in the elderly. This includes the challenges of diagnosing and treating epilepsy in the aging population in the clinical setting.

Neuroplastic changes in the aged brain

There are several well-documented neuroplastic changes in the aged brain. Specifically, decreased synapse density in the molecular layer of the dentate gyrus [7] and decreased production of newly born dentate granule cells [8]. This decrease in neurogenesis is further supported by Shapiro et al [9]. Despite this diminished baseline neurogenesis in the aged brain, Shapiro et al. [9] demonstrate that seizures in the aging brain result in a significant increase in hippocampal neurogenesis relative to age-matched controls. In addition, Shapiro et al. [9] demonstrate the dysmorphic appearance of the newborn granule cells after pilocarpine-induced seizures in the aging brain, including the appearance of basal dendrites. It is interesting to note that a previous study indicates that the number of progenitor cells is not decreased in aging [10], but there is a decrease in progenitor cell proliferation factors [11]. Thus, it appears as though there is still a neurogenic potential in the aged brain, but other factors such as astrocytes and their secretions are altered. Further evidence for the alteration to astrocytes in the hippocampus of the aged epileptic brain is demonstrated in this special edition by Arisi et al. [12].

Within the hippocampus of elderly humans, seizures can result in cell loss [13] and induce mossy fibers to aberrantly sprout into the inner molecular layer [14]. This aberrant neuroplasticity has been duplicated in aged rodent models of temporal lobe epilepsy and was shown to alter local circuit neurons and increase seizure susceptibility [15]. In the article by Cavarsan et al. [16], the authors show that m1 muscarinic acetylcholine receptors are decreased in the CA1 region of the hippocampus following pilocarpine-induced seizures in aged rats.

Long-term potentiation (LTP) is also affected with age, especially in the dentate gyrus, where NMDA-receptor dependent LTP is reduced and voltage dependent calcium channel LTP is increased [17]. In

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addition, kindling is altered in the aged-brain [18]. Thus, there is pathology, neuroplasticity and excitability in the epileptic aged brain. These results are expanded upon in a series of electrophysiological studies featured in this special edition. First, Wedine et al. [19] demonstrate that chronic BDNF over-expression throughout the life-span can cause spontaneous seizures to occur in the aging rodent brain. They also demonstrated that chronic over-expression of BDNF resulted in increased NPY expression in the mossy fiber pathway in the aged BDNF transgenic mice [19]. Moreover, epileptiform activity was demonstrated in response to either repeated paired pulse or high frequency stimulation in CA3 of the aged BDNF-transgenic mice, but not in age-matched wild-type controls [19]. Continuing the theme of altered CA3 excitability, Kanak et al. [20] demonstrate that repetitive electrical stimulation of the hilus, or bath application of kainic acid, more readily elicited excitable network activity in CA3 of aged F344 rats, as compared to adult rats, despite the fact that basal activity was comparable between the two ages. In a separate study, Zhang et al. [21] used kanic acid to induce-seizures in young adult rats that were allowed to survive until 2 years of age. Analysis at this late-life timepoint showed altered excitability in CA1 as well as frequent interictal spikes in the subiculum. In these rats, Topiramate was shown to inhibit action potential firing [21].

Taken together, this collection of studies demonstrates altered anatomical and physiological functioning of the aged brain. Some of these changes are similar to those seen in young adult rodents, while others are quite different. Considering the co-morbidity, cognitive, metabolic, neuroplastic and electrophysiological differences in aging, as well as the high incidence rate of seizures and epilepsy in the aging population, there is a pressing need for expanded study into epileptogenic mechanisms in the aging brain. This demand is further necessitated by the fact that the population density of adults over the age of 65 is increasing at a rapid rate.

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